V SIMPOSIO GETHI 18/19 noviembre de 2019
Ilustre Colegio Oficial de Médicos de Madrid. Aula Jiménez Díaz. Madrid

# FGFR Inhibitors: Clinical Evidence

Ignacio Duran, MD,PhD
Hospital Universitario Marques de Valdecilla
IDIVAL
Santander. Cantabria

Valdecilla Instituto de Investigación Sanitaria IDIVAL
humv HOSPITAL UNIVERSITARIO MARQUÉS DE VALDECILLA

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# FGFR Inhibitors: Clinical Evidence **of a new targeted therapy**

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# Learning Objectives

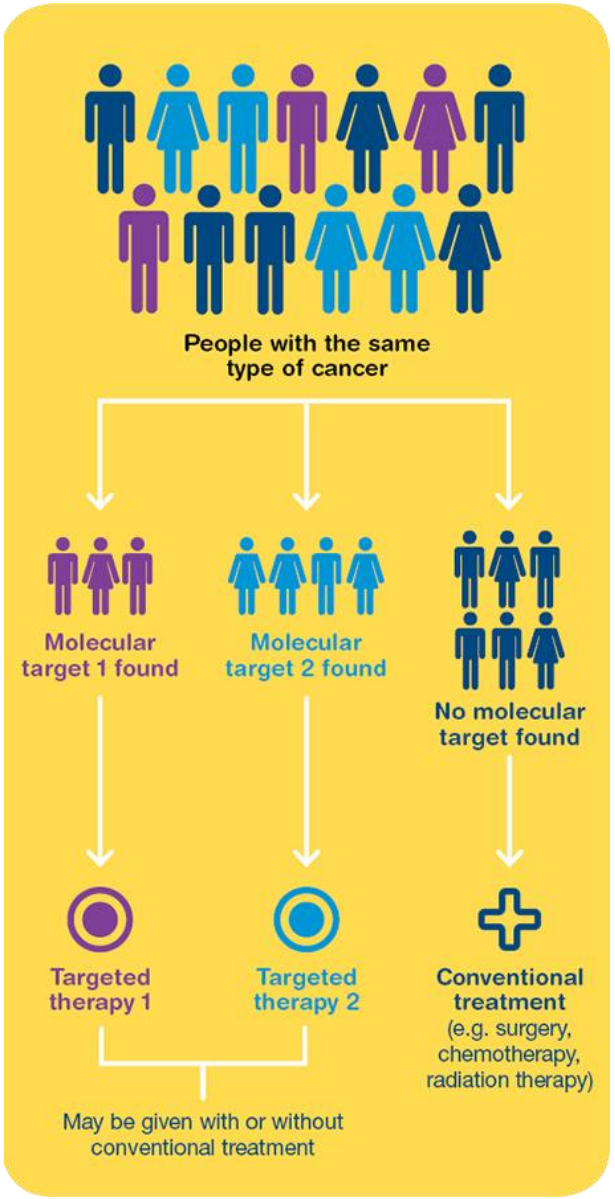
- To briefly review the **rationale** behind the development of a **targeted therapy** centred in **FGFR**

- To present the most recent **clinical evidence** around FGFR inhibition in cancer with a particular focus on **urothelial cancer [**and a brief note on **cholangiocarcinoma]**

- To discuss current **limitations** and **further development** of FGFR inhibition

# Outline

- Introduction: Targeted therapy myth or reality?
- Developing a targeted therapy: Key steps
- The case of FGFR inhibition
  - Biological plausibility
  - Predictive biomarkers
  - Selective compounds
  - Efficacy
  - Safety
- Limitations of FGFR inhibition
- Questions and answers




# Targeted Therapy: Is there a real clinical evidence?

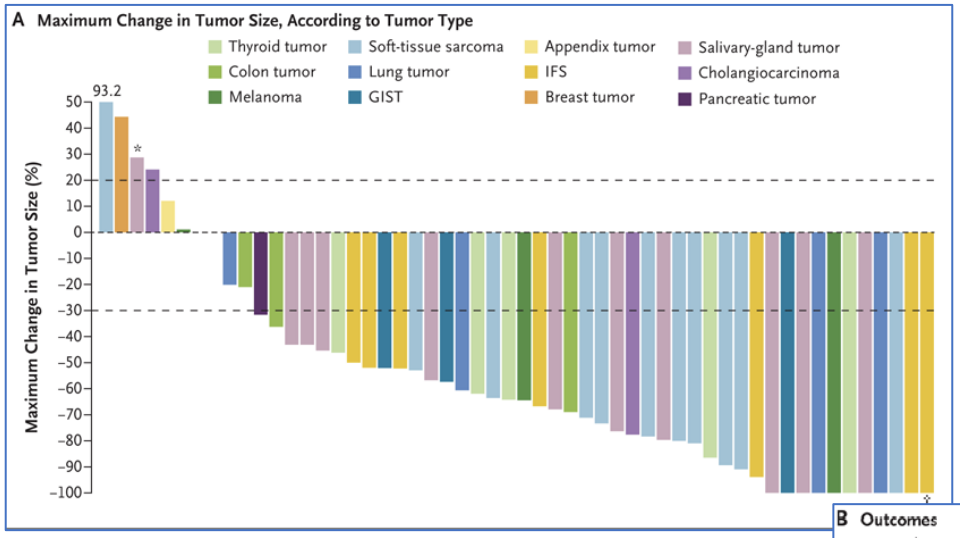
Is Targeted Therapy such as FGFR inhibition ready for Prime Time?

Are we overcoming some previously identified barriers ?

Is FGFR a good target for anti cancer treatment?

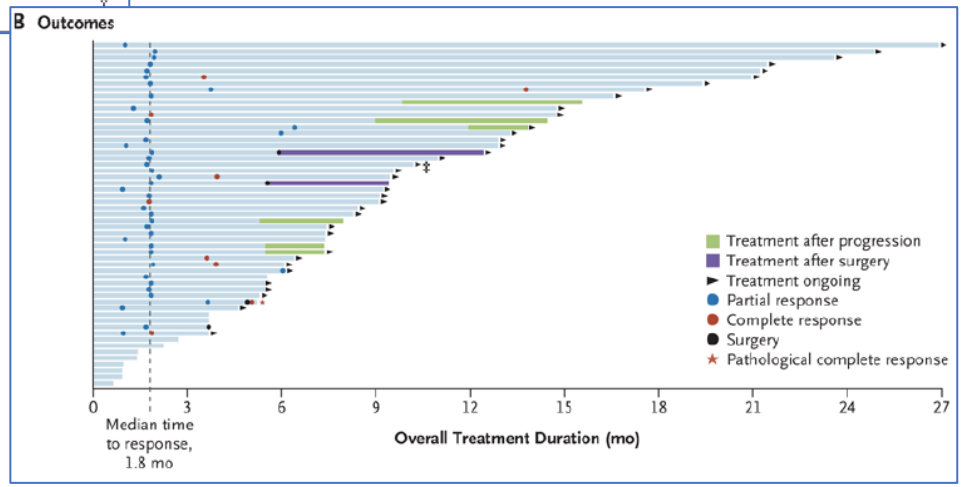
Limits to Personalized Cancer Medicine Tannock IF et al N Engl J Med 375;13; 2016

# Targeted Therapy: Recent “successful” stories



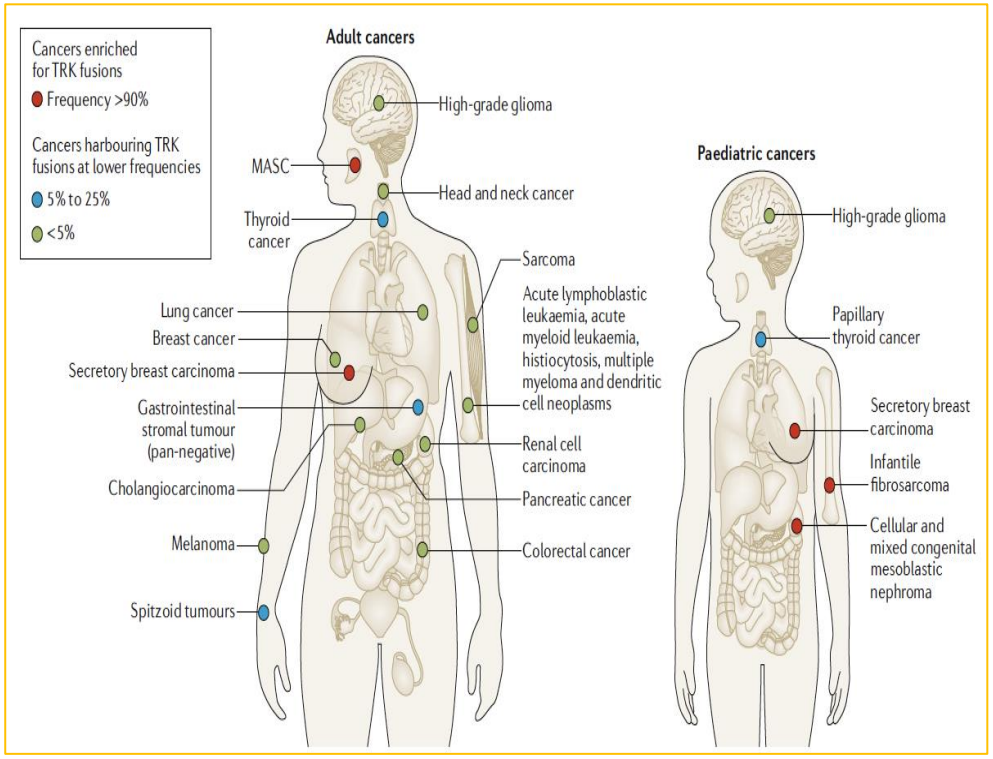

Patients had **17** unique TRK fusion–positive **tumor types**.
ORR : 75% according to independent review and 80% (95% CI, 67 to 90) according to investigator assessment.

Larotrectinib had marked and durable antitumor activity in patients with TRK fusion–positive cancer, regardless of the age of the patient or of the tumor type.

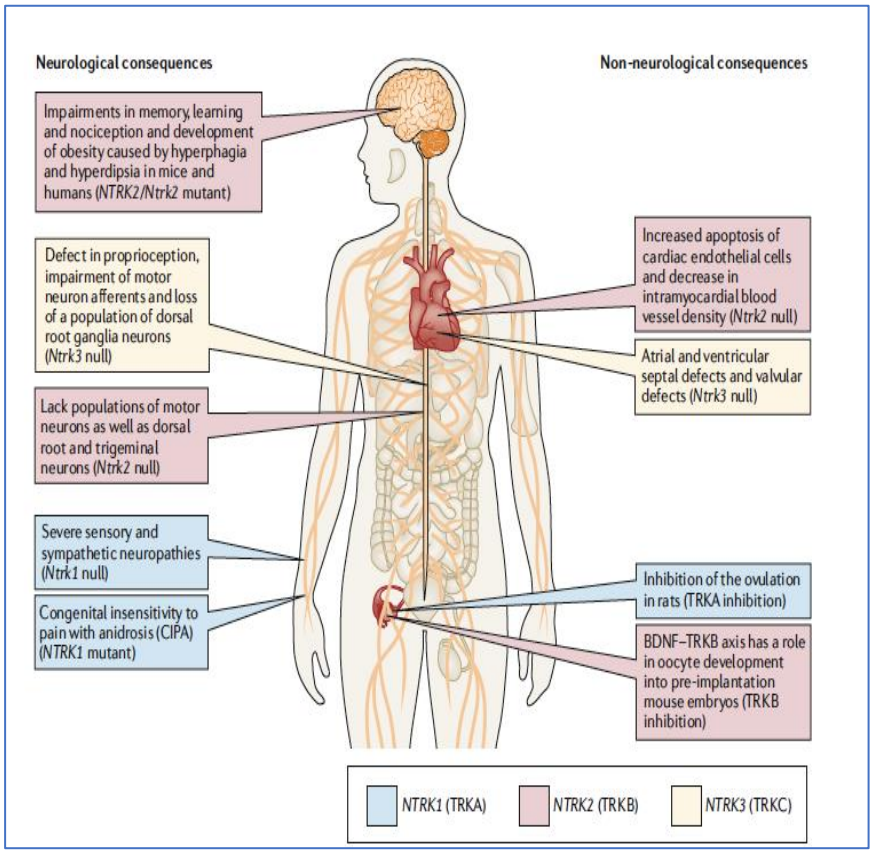



Drilon A, Laetsch TW, Kummar S, DuBois SG, Lassen UN, Demetri GD, et al. Efficacy of larotrectinib in TRK fusion–positive cancers in adults and children. N Engl J Med 2018;378:731-9.

# Targeted Therapy: Limitations




Distribution and frequency of NTRK fusions in adult and paediatric tumours




Consequences of loss, decreased activity or inhibition of TRK

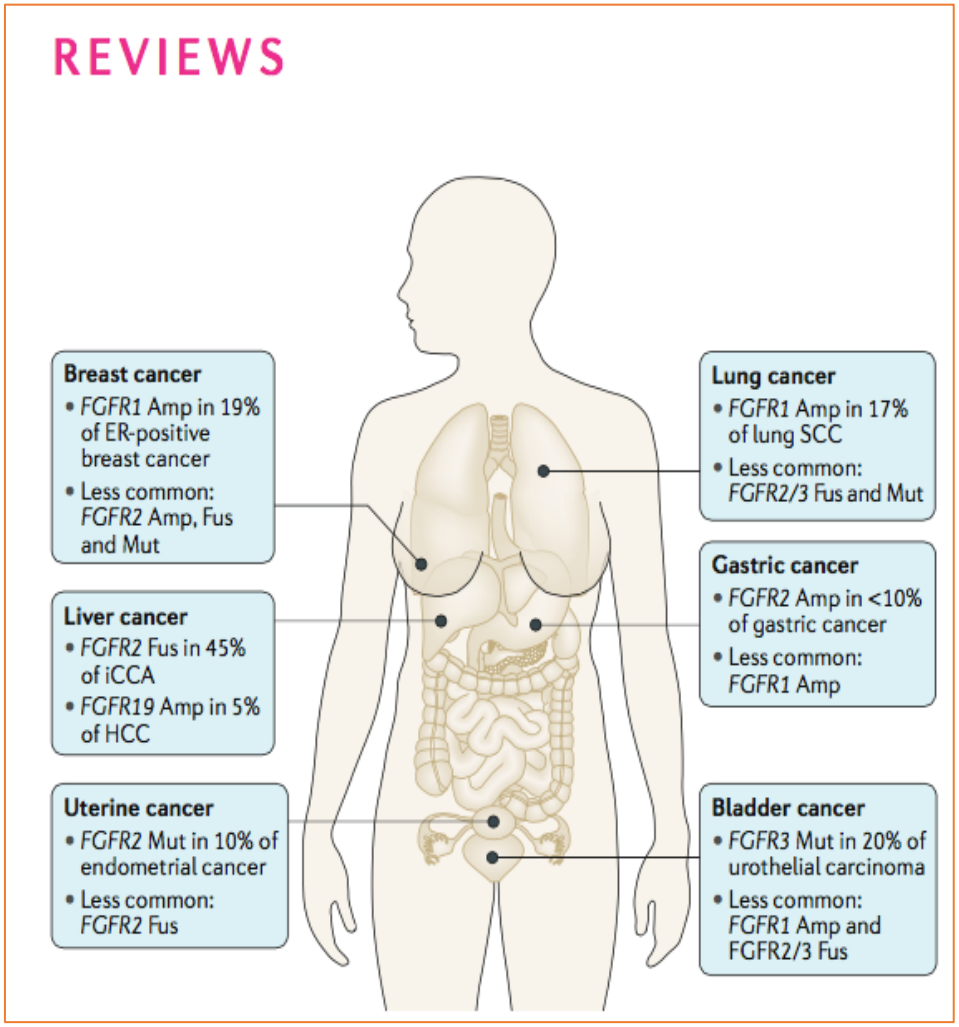
How relevant is the target in the population and how tolerable is the targeted therapy?

Cocco E et al Nature Reviews Clinical Oncology 2018

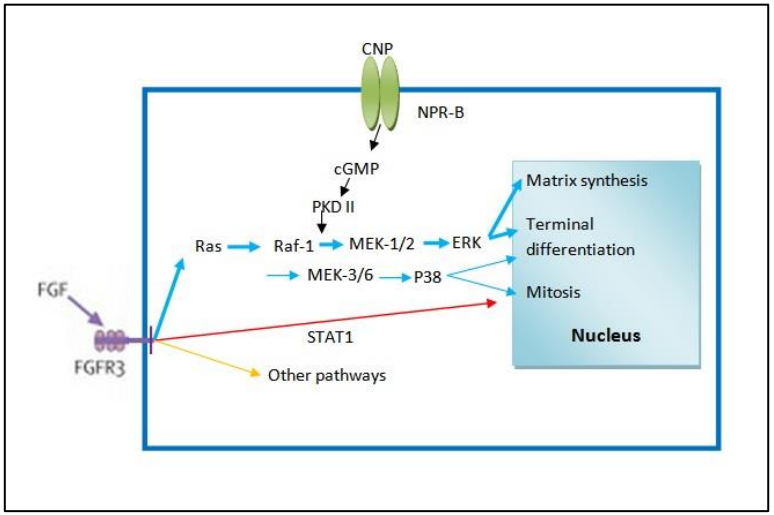
# What is key in building a successful targeted therapy?

- Having a target with demonstrated implication in cancer biology
  - **BIOLOGICAL PLAUSIBILITY**
- Being able to identify those patients more likely to benefit
  - **DEFINITION OF A VALID PREDICTIVE BIOMARKER**
- Developing the proper family of compounds
  - **SPECIFIC COMPOUNDS**
- Being able to show anti tumour activity
  - **EFFICACY**
- Being a target whose block is tolerable
  - **SAFETY/TOXICITY**

# Biological plausability




- The altered **FGFR gene expression** may enhance several **cancer-promoting cell functions** such as <u>cell division</u> (proliferation), <u>cell movement,</u> and the <u>formation of new blood vessels</u> that nourish a growing tumor.




- Extensively reviewed by Dr. Sevillano

*Masaru Katoh, Nature Reviews 2018*

# Biological plausability

- A recent analysis of 412 cases of **muscle-invasive bladder cancer** within The Cancer Genome Atlas (TCGA) identified 784 gene fusions in these samples, of which **FGFR3-TACC3** was the most common .

- Additionally, fusions between FGFR2 and AHCYL1 or BICC1 have been identified in 14% of cases of **intrahepatic cholangiocarcinoma (**CCA), which have been associated not only with oncogenic potential but also sensitivity to FGFR inhibition

Arai Y, et al. Fibroblast growth factor receptor 2 tyrosine kinase fusions define a unique molecular subtype of cholangiocarcinoma. Hepatology 2014;59:1427-34. Robertson AG, et al; TCGA Research Network, Weinstein JN, Kwiatkowski DJ, Lerner SP. Comprehensive molecular characterization of muscle-invasive bladder cancer. Cell 2017;171:540-56.

# Predictive biomarker

- The molecular screening to identify patients suitable for treatment with selective FGFR inhibitors is currently seeking for cases with **gene fusions** (very infrequent) **and mutations** ( variable frequency across tumor types)

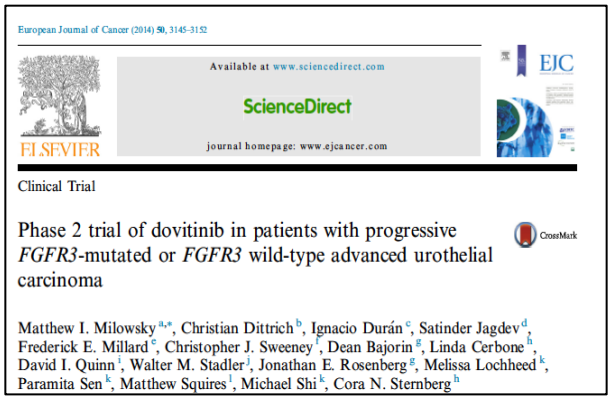
- **Amplifications** do not seem to predict well for efficacy

# Development of anti-FGFR compounds

- **First-generation FGFR-TKI** (ponatinib, dovitinib, lucitanib, lenvatinib, nintedanib) operate as **multi-target inhibitors**, including FGFR among their wide range of hits (VEGFR1/3, KIT, RET among others).

- This led to the **lack of a profound anti-FGFR inhibition** and to the occurrence of deleterious adverse events: First disappointments

# First attempts: Dissapointments



European Journal of Cancer (2014) 50, 3145-3152

Available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Clinical Trial

Phase 2 trial of dovitinib in patients with progressive *FGFR3*-mutated or *FGFR3* wild-type advanced urothelial carcinoma

Matthew I. Milowsky[a,*], Christian Dittrich[b], Ignacio Durán[c], Satinder Jagdev[d], Frederick E. Millard[c], Christopher J. Sweeney[f], Dean Bajorin[g], Linda Cerbone[h], David I. Quinn[i], Walter M. Stadler[j], Jonathan E. Rosenberg[g], Melissa Lochheed[k], Paramita Sen[k], Matthew Squires[l], Michael Shi[k], Cora N. Sternberg[h]

1st Generation FGFR Inhibitors did not fulfill expectations

Neither in efficacy nor as a predictive biomarker

Best overall tumour response by *FGFR3* mutation status, as determined by investigator and central radiology review.

| Clinical response | $FGFR3^{MUT}$ ($n = 12$) | $FGFR3^{WT}$ ($n = 31$) |
|---|---|---|
| Investigator review, *n* (%) | | |
| CR | 0 | 0 |
| PR | 0 | 1 (3) |
| SD | 5 (42) | 10 (32) |
| PD | 5 (42) | 12 (39) |
| UNK | 2 (17) | 8 (26) |
| ORR (CR + PR) | 0 | 1 (3) |
| DCR[a] | 3 (25) | 8 (26) |
| 95% CI for ORR | (0.0–26.5) | (0.1-16.7) |
| 95% CI for DCR | (5.5–57.2) | (11.9-44.6) |
| Central radiology review, *n* (%) | | |
| CR | 0 | 0 |
| PR | 1 (8) | 0 |
| SD | 3 (25) | 12 (39) |
| PD | 6 (50) | 9 (29) |
| UNK | 2 (17) | 10 (32) |
| ORR (CR + PR) | 1 (8) | 0 |
| DCR[a] | 2 (17) | 9 (29) |
| 95% CI for ORR | (0.2–38.5) | (0.0–11.2) |
| 95% CI for DCR | (2.1–48.4) | (14.2–48.0) |

In conclusion, although generally well tolerated, dovitinib appears to have very limited single-agent activity in previously treated patients with advanced UC, regardless of *FGFR3* mutation status. Although these results do not support further investigation of single-agent dovitinib, studies evaluating more potent FGFR3 inhibitors are warranted.

Table 3
Adverse events suspected to be related to the study drug in >10% of patients (all grades).[a]

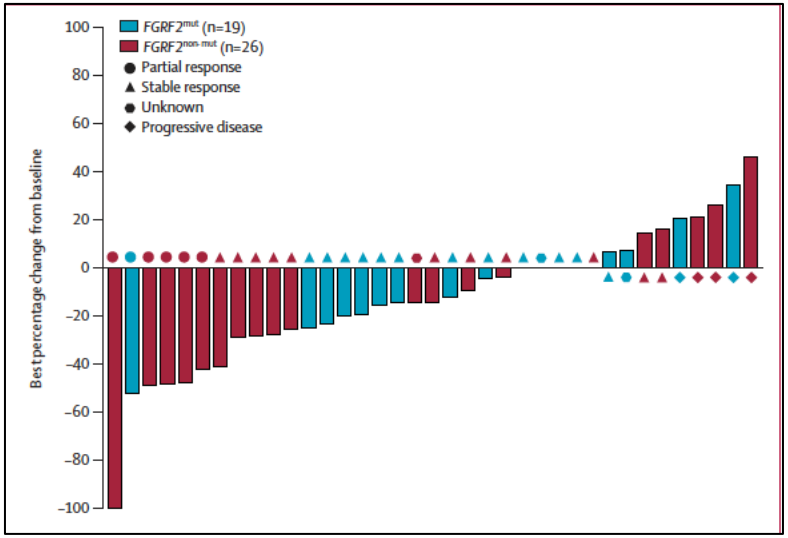
| Adverse event | All patients ($N = 44$) | | |
|---|---|---|---|
| Preferred term, *n* (%) | Any grade | Grade 3 | Grade 4 |
| Any | 41 (93) | 25 (57) | 3 (7) |
| Diarrhoea | 29 (66) | 3 (7) | 0 |
| Nausea | 26 (59) | 0 | 0 |
| Decreased appetite | 16 (36) | 0 | 0 |
| Vomiting | 16 (36) | 1 (2) | 0 |
| Fatigue | 14 (32) | 4 (9) | 0 |
| Asthenia | 13 (30) | 4 (9) | 0 |
| Rash | 10 (23) | 2 (5) | 0 |
| Anaemia | 7 (16) | 2 (5) | 0 |
| Thrombocytopenia | 7 (16) | 3 (7) | 1 (2) |
| Alanine aminotransferase increased | 6 (14) | 1 (2) | 1 (2) |
| Hypertension | 6 (14) | 0 | 0 |
| Aspartate aminotransferase increased | 5 (11) | 1 (2) | 1 (2) |
| Constipation | 5 (11) | 1 (2) | 0 |
| Dysgeusia | 5 (11) | 0 | 0 |

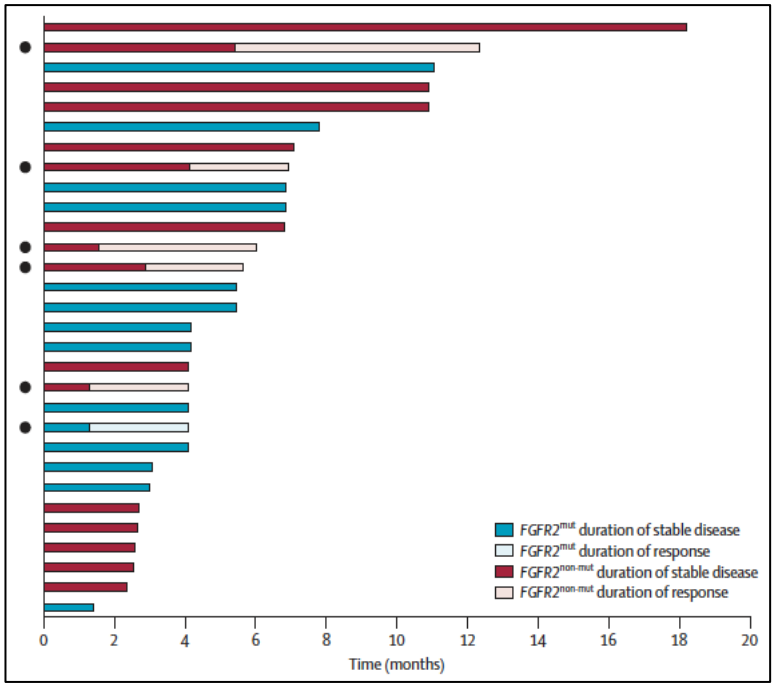
[a] Patients with multiple occurrences of an adverse event are counted only once at the highest grade.

# First attempts: Doubts

**Second-line dovitinib (TKI258) in patients with *FGFR2*-mutated or *FGFR2*-non-mutated advanced or metastatic endometrial cancer: a non-randomised, open-label, two-group, two-stage, phase 2 study**

*Gottfried E Konecny, Neil Finkler, Agustin A Garcia, Domenica Lorusso, Paula S Lee, Rodney P Rocconi, Peter C Fong, Matt Squires, Kaushal Mishra, Allison Upalawanna, Yongyu Wang, Rebecca Kristeleit*




*"…Observed **treatment effects** seemed **independent of FGFR2 mutation status**…Additional studies are needed"*

Unfortunately, our study was not able to establish whether the effects seen in the *FGFR2*$^{mut}$ group were due to FGFR2 inhibition only or also due to the anti-angiogenic effects from FGFR1, FGFR2, FGFR3, VEGFR1, VEGFR2, VEGFR3, and PDGFR-β as seen in the *FGFR2*$^{non\text{-}mut}$ group. A clinical trial with a more

# Further Drug Development: Next Generation FGFR Inhibitors

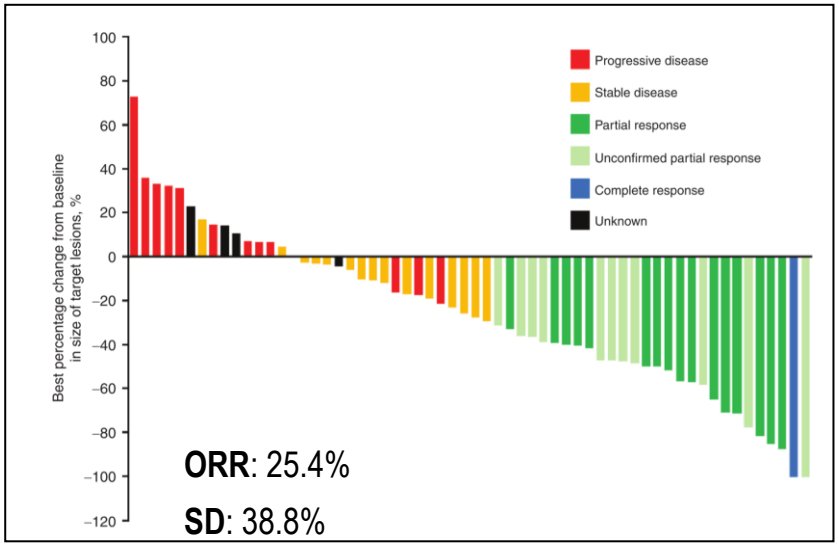
- Better patient selection has led to a more precise drug development around FGFR inhibition
- Around 12-15 compounds are in different stages of development in the clinic
- Most of the development in later stages in focused in bladder and HCC

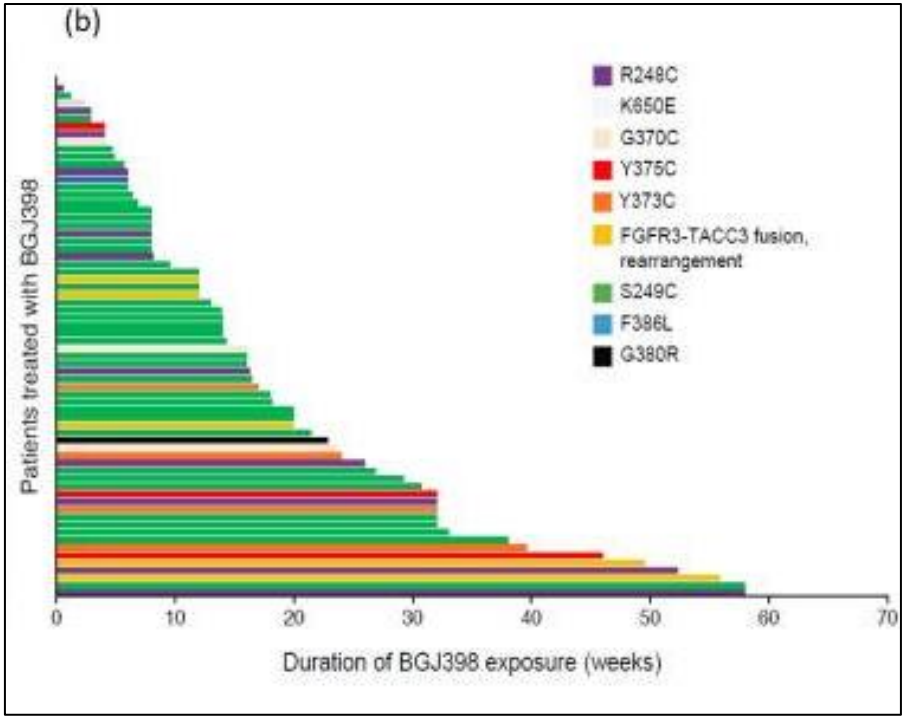
| Drug | Target | Inhibition Type | Ongoing Trials |
|---|---|---|---|
| **Infigratinib BGJ 398** | FGFR 1-3 | Reversible | Phase III |
| **Rogaratinib BAY 116387** | FGFR 1-3 | Reversible | Phase III |
| **Erdafitinib JNJ42756493** | FGFR 1-4 | Reversible | Phase III |
| **Pemigatinib INCB053828** | FGFR 1-3 | Reversible | Phase III |
| **TAS-120** | FGFR 1-4 | Covalent | Phase II |
| **Derazantinib ARQ 087** | FGFR 1-4 | Reversible | Phase II |
| **LY2874455** | FGFR 1-4 | Reversible | Phase I |
| **AZD4547** | FGFR 1-3 | Reversible | Phase II |
| **Debio 1347** | FGFR 1-3 | Reversible | Phase II |
| **BLU- 554** | FGFR 4 | Irreversible | Phase I ext |
| **B-701** | FGFR3 | mAB | Phase II |

Table modified from Facchinetti F et al Clin Can Res 2019

# Infigratinib [BGJ398]

**67 patients with mUC and FGFR3 mutations**




| Variable, n (%) | | Participants (N=67) |
|---|---|---|
| | | |
| **Sex** | Male | 46 (68.7) |
| | Female | 21 (31.3) |
| **WHO performance status** | 0 | 20 (29.9) |
| | 1 | 36 (53.7) |
| | 2 | 10 (14.9) |
| | Missing | 1 (1.5) |
| | | |
| **Visceral disease** | Lung | 41 (61.2) |
| | Liver | 25 (37.3) |
| **Lymph node metastases** | Yes | 19 (28.4) |
| | No | 46 (68.7) |
| | Missing | 2 (3) |
| | | |
| **Prior immunotherapy at last medication** | | 11 (16.4) |
| **FGFR3 status** | Not mutated | 0 |
| | Mutated[b] | 67 (100) |
| | Exon 7 R248C | 11 (16.4) |
| | Exon 7 S249C | 38 (56.7) |
| | Exon 10 Y375C | 3 (4.5) |
| | Exon 15 K625E/Q | 0 |
| | Other[b] | 15 (22.4) |

- Median PFS: 3.75 mos; Median OS 7.75 mos; Median DoR: 5.06 mos

Nineteen patients (28.4%) had received one prior antineoplastic therapy, and 47 patients (70.1%) had received ≥ 2; one patient was treatment naive.

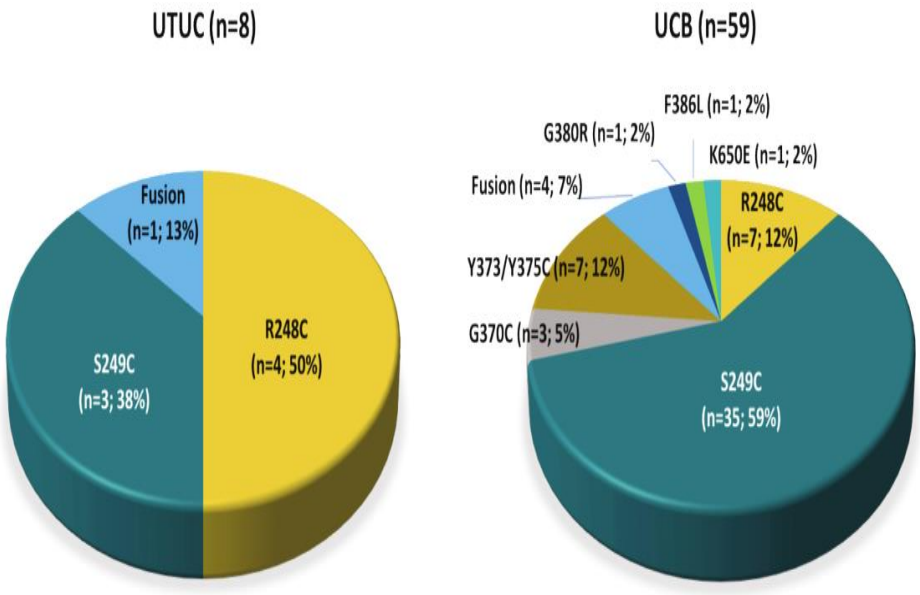
The most common TRAEs were **hyperphosphatemia**, e**levated creatinine**, **fatigue, constipatio**n and decreased appetite.

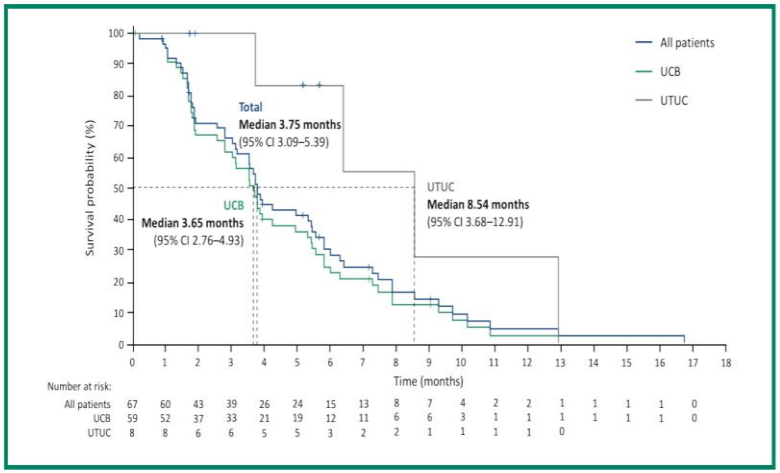
**Further examination** of BGJ398 in this disease setting is **warranted.**

Pal SK, *et al.* Cancer Discovery 2018 , Efficacy of BGJ398, a Fibroblast Growth Factor Receptor 1–3 Inhibitor, in Patients with Previously Treated Advanced Urothelial Carcinoma with FGFR3 Alterations,

# Infigratinib: Does location matters?

- Patients with UTUC vs BC have  different molecular profile and  superior outcomes




| | UTUC (n=8) | UCB (n=59) | Total (n=67) |
|---|---|---|---|
| Confirmed objective response (CR or PR), n (%) | 4 (50.0) | 13 (22.0) | 17 (25.4) |
| 95% CI | 15.7–84.3 | 12.3–34.7 | 15.5–37.5 |
| Disease control rate (CR/PR or SD), n (%) | 8 (100.0) | 35 (59.3) | 43 (64.2) |
| 95% CI | 63.1–100.0 | 45.7–71.9 | 51.5–75.5 |
| Median duration of response, months | 6.77 | 5.04 | 5.62 |
| Range* | 3.32+ – 11.01 | 2.33+ – 8.08 | 2.33+ – 11.01 |

'+: patients who have a confirmed objective response without an assessment of disease progression/deaths are included as 'censored'

- R248C mutations more common (50%)
- Fusions more common (13%)
- Is it worth it to focus on UTUC?

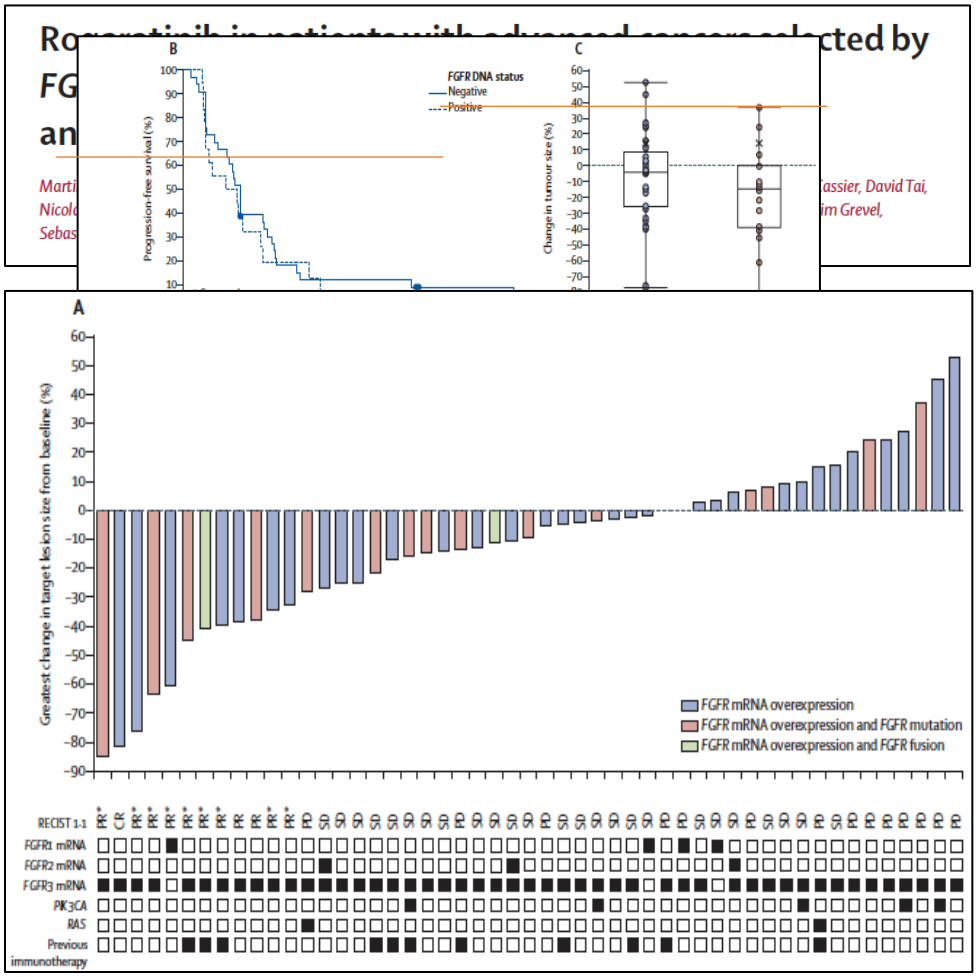
Dizman N, *et al.* J Clin Oncol 37, 2019:(suppl; abstr 4510). Presented at ASCO 2019.

# Rogaratinib

| | Dose-escalation cohort (n=23) | Dose-expansion cohort (n=103) | | | | All enrolled patients (n=126) |
|---|---|---|---|---|---|---|
| | | Urothelial carcinoma (n=52) | Head and neck squamous cell carcinoma (n=8) | Non-small-cell lung cancer (n=20) | Other solid tumours (n=23) | |
| Sex | | | | | | |
| Men | 14 (61%) | 37 (71%) | 8 (100%) | 18 (90%) | 14 (61%) | 91 (72%) |
| Women | 9 (39%) | 15 (29%) | 0 | 2 (10%) | 9 (39%) | 35 (28%) |
| Race | | | | | | |
| White | 19 (83%) | 36 (69%) | 7 (88%) | 10 (50%) | 15 (65%) | 87 (69%) |
| Asian | 4 (17%) | 11 (21%) | 1 (13%) | 10 (50%) | 8 (35%) | 34 (27%) |
| Not reported | 0 | 5 (10%) | 0 | 0 | 0 | 5 (4%) |
| Age, years | 62·0 (45·0–67·0) | 67·5 (60·0–73·0) | 67·0 (56·0–71·0) | 61·0 (57·0–67·0) | 62·0 (57·0–71·0) | 63·5 (58·0–71·0) |
| ECOG performance status | | | | | | |
| 0 | 9 (39%) | 13 (25%) | 3 (38%) | 6 (30%) | 10 (43%) | 41 (33%) |
| 1 | 12 (52%) | 37 (71%) | 5 (63%) | 12 (60%) | 12 (52%) | 78 (62%) |
| 2 | 2 (9%) | 2 (4%) | 0 | 2 (10%) | 1 (4%) | 7 (6%) |

Data are n (%) or median (IQR). ECOG=Eastern Cooperative Oncology Group.

- Patients selected based on **<u>mRNA overexpression</u>** (Not only mutations or fusions)
- Larger proportion of patients tested positive [around 50%]




Tumour responses to rogaratinib in the urothelial carcinoma dose-expansion cohort (n=52)

- **Rogaratinib** in patients selected by FGFR overexpressing cancers resulted in a manageable **safety profile** and **encouraging antitumour activity**, even in patients refractory to IO
- **FGFR mRNA overexpression** could be a clinically useful biomarker in addition to genetic alterations, identifying more patients who are likely to be susceptible to FGFR inhibition.

# Rogaratinib: Near Future

- Efficacy?
- Safety
- Biomarker?

## Ongoing Clinical Trials With Rogaratinib

| PHASE | STATUS | DESCRIPTION | TUMOR TYPE |
|---|---|---|---|
| II/III | ACTIVE, NOT ENROLLING | **FORT-1:** A Phase II/III Study to Evaluate the Efficacy and Safety of Rogaratinib (BAY 1163877) Compared to Chemotherapy in Patients With FGFR-positive Locally Advanced or Metastatic Urothelial Carcinoma Who Have Received Prior Platinum-containing Chemotherapy (NCT03410693) | FGFR-positive locally advanced or metastatic urothelial carcinoma |
| I/II | NOW ENROLLING | **FORT-2:** An International, Multicenter, Phase Ib/II Study of Rogaratinib (BAY 1163877) in Combination With Atezolizumab as First-line Treatment in Cisplatin-ineligible Patients With FGFR-positive Locally Advanced or Metastatic Urothelial Carcinoma (NCT03473756) | FGFR-positive locally advanced or metastatic urothelial carcinoma |
| I | NOW ENROLLING | **ROCOCO:** A Multicenter Phase I Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Maximum Tolerated Dose (MTD) and/or Recommended Phase II Dose (RP2D) of the Combination of Rogaratinib and Copanlisib in Patients with FGFR-positive, Locally Advanced or Metastatic Solid Tumors (NCT03517956) | FGFR-positive locally advanced or metastatic solid tumors |

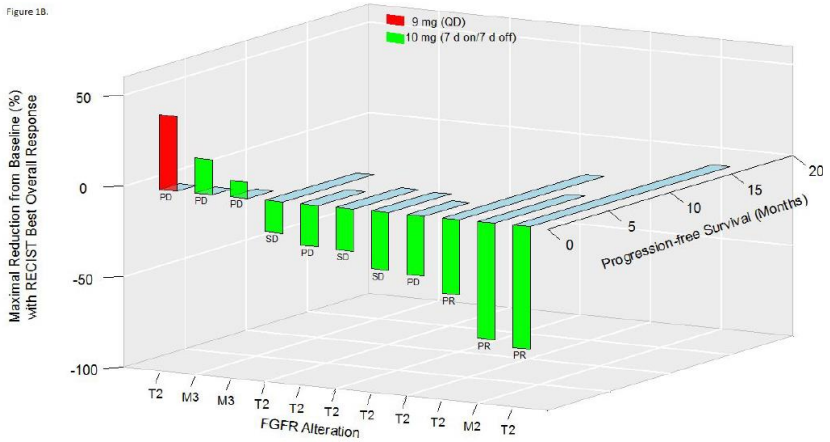
# ERDAFITINIB

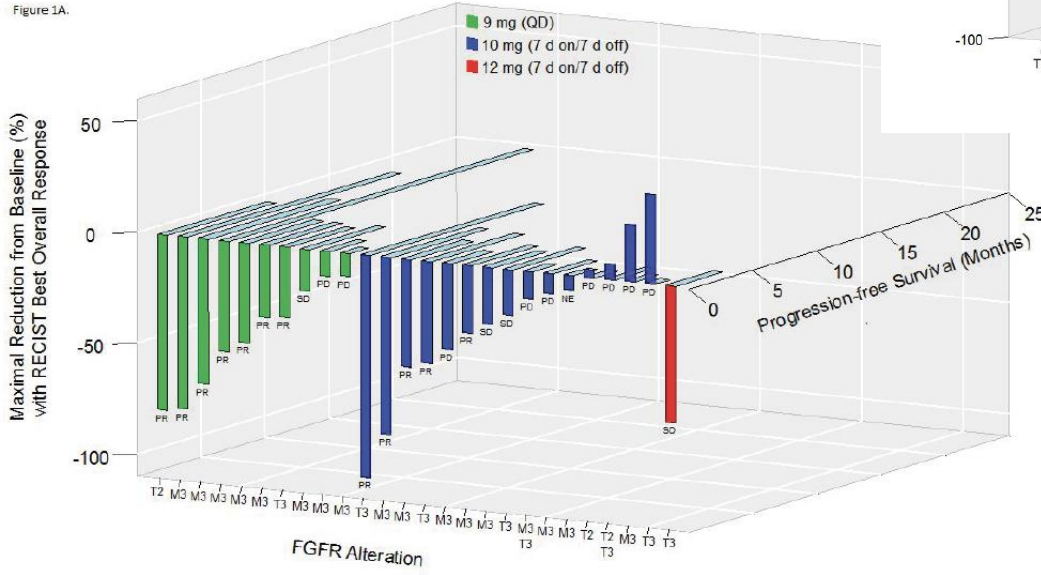
1st signals on Phase I study:

**Multicenter Phase I Study of Erdafitinib (JNJ-42756493), Oral Pan-Fibroblast Growth Factor Receptor Inhibitor, in Patients with Advanced or Refractory Solid Tumors**

Rastilav Bahleda, Antoine Italiano, Cinta Hierro, et al.

*Clin Cancer Res* Published OnlineFirst May 14, 2019.



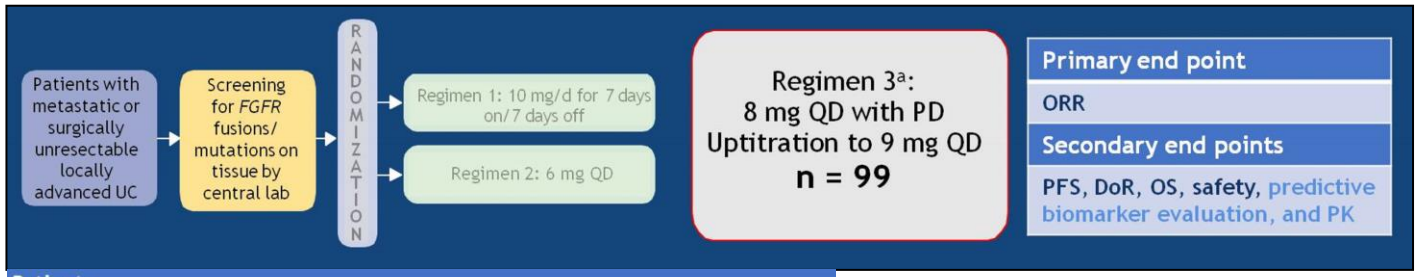




| Patients treated | Objective responses | Stable Diseases | mPFS (mo) (95% CI) | mDOR (mo) (95% CI) |
|---|---|---|---|---|
| 27 $FGFR^{pos}$ ($17\ FGFR3^{mut}$, $11\ FGFR^{fused}$, $1\ FGFR^{mut+fused}$) out of 30 UC | 12/30 (40%) among all UC<br>12/26 (46%) among $FGFR^{pos}$ | $FGFR^{pos}$: 4/26 (15%) | $FGFR^{mut/fused}$: 5.1 | 5.6 |

All patients with UC and CCA who responded to treatment with erdafitinib carried FGFR mutations or gene fusions

Erdafitinib shows tolerability and **preliminary evidence of clinical activity** in advanced solid tumors, at 2 different dosing schedules and with particularly encouraging responses in UC and CCA.

# Erdafitinib: Phase II




**Patients**

- Progression on ≥ 1 line prior systemic chemo or within 12 months of (neo)adjuvant chemo OR
- Chemo-naïve: cisplatin ineligible per protocol criteria[b]
- Prior immunotherapy was allowed

[a]Dose uptitration if ≥ 5.5 mg/dL target serum phosphate not reached by Day 14 and if no TRAEs.
[b]Ineligibility for cisplatin: impaired renal function or peripheral neuropathy.

- Heavily pre-treated group of pts
- Poor prognosis group

| Patients, n (%) | | 8 mg continuous dose (n = 99) |
|---|---|---|
| Age, median years (range) | | 68 (36-87) |
| ECOG performance status | 0 | 50 (51) |
| | 1 | 42 (42) |
| | 2 | 7 (7) |
| Pre-treatment | Progressed or relapsed after chemo | 87 (88) |
| | Chemo-naïve | 12 (12) |
| | Prior immunotherapy | 22 (22) |
| Number of lines of prior treatment | 0 | 11 (11) |
| | 1 | 45 (46) |
| | 2 | 29 (29) |
| | ≥ 3 | 14 (14) |
| Visceral metastases | Present | 78 (79) |
| | Absent | 21 (21) |
| Hemoglobin Level | ≥10 | 84 (85) |
| | <10 | 15 (15) |
| Tumor location | Upper tract | 23 (23) |
| | Lower tract | 76 (77) |
| Creatinine clearance rate | < 60 mL/min | 52 (53) |
| | ≥ 60 mL/min | 47 (47) |
| *FGFR* alterations | *FGFR2* or *FGFR3* fusion | 25 (25) |
| | *FGFR3* mutation | 74 (75) |

**Primary hypothesis:**

- ORR in Regimen 3 is > 25%
- One-sided α = 0.025
- 85% power

- Mostly FGFR3 mutations
- Also fusions FGFR2/3

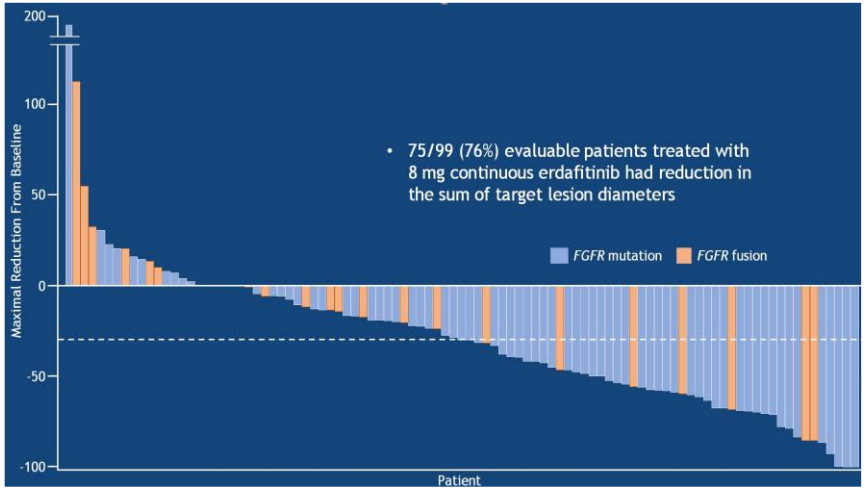
Siefker-Radtke A, *et al.* J Clin Oncol 36, 2018 (suppl; abstr 4503). Presented at ASCO 2018 Annual Meeting. Reproduced with permission from Dr A Siefker-Radtke.

# Erdafitinib activity

| | | [95% CI] |
|---|---|---|
| Patients, n | 99 | |
| Response per investigator assessment[a,b], n (%) | | |
| ORR | 40 (40.4) | [30.7-50.1] |
| Complete response | 3 (3.0) | |
| Partial response | 37 (37.4) | |
| Stable disease | 39 (39.4) | |
| Progressive disease | 18 (18.2) | |
| Median time to response | 1.4 months | |
| Median duration of response | 5.6 months | [4.2-7.2] |
| ORR among patient subgroups, n (%) | | |
| Chemo-naïve vs progressed/relapsed after chemo | 5/12 (41.7) vs 35/87 (40.2) | |
| With vs without visceral metastases | 30/78 (38.5) vs 10/21 (47.6) | |

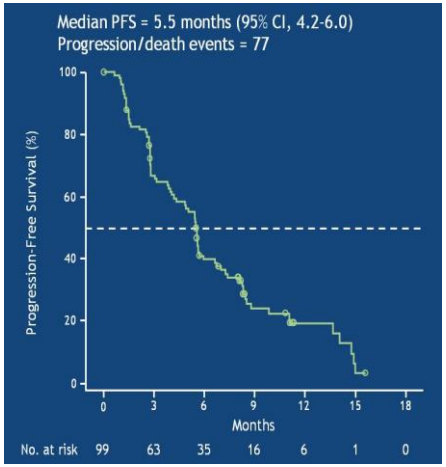
[a]Confirmed with second scan at least 6 weeks following the initial observation of response.
[b]Response in 2 patients was unknown.

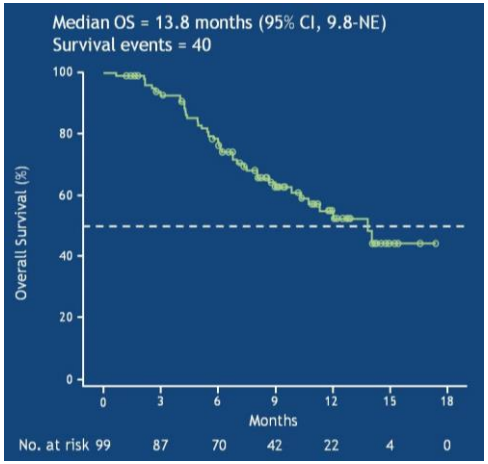
21.2% of patients remain on study treatment after 11 months of follow-up




After previous positive data [Loriot Y; ASCO GU 2018]
It was confirmed that Erdafitinib provides:

- Remarkable response rates and SD
- Activity even in "bad patients' [visceral mets]
- Short time to response (1.4 months)
- PFS 5.5 mos
- OS 13.8 mos
- DOR?




Siefker-Radtke A, et al. J Clin Oncol 36, 2018 (suppl; abstr 4503). Presented at ASCO 2018 Annual Meeting; Updated at ASCO 2019 by SH Park et al. J Clin Oncol 37, 2019 (suppl; abstr 4543). Presented at ASCO 2019 Annual Meeting. Reproduced with permission from Dr A Siefker-Radtke.

# Regulatory Approval

- FDA grants accelerated approval to erdafitinib for metastatic urothelial carcinoma

- On April 12, 2019, the Food and Drug Administration granted accelerated approval to erdafitinib (BALVERSA, Janssen Pharmaceutical Companies) for patients with locally advanced or metastatic urothelial carcinoma, **with susceptible FGFR3 or FGFR2 genetic alterations,** that has progressed during or following platinum-containing chemotherapy, including within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy.

- Patients should be selected for therapy based on an FDA-approved companion diagnostic for erdafitinib.

- Today, the FDA also approved the ***therascreen®*** **FGFR RGQ RT-PCR Kit**, developed by QIAGEN, for use as a **companion diagnostic** for this therapeutic indication.

Available at: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-erdafitinib-metastatic-urothelial-carcinoma. Accessed Sept 2019

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

# Erdafitinib in Locally Advanced or Metastatic Urothelial Carcinoma

Y. Loriot, A. Necchi, S.H. Park, J. Garcia-Donas, R. Huddart, E. Burgess, M. Fleming, A. Rezazadeh, B. Mellado, S. Varlamov, M. Joshi, I. Duran,

National Comprehensive Cancer Network®

## NCCN Guidelines Version 4.2019
## Bladder Cancer

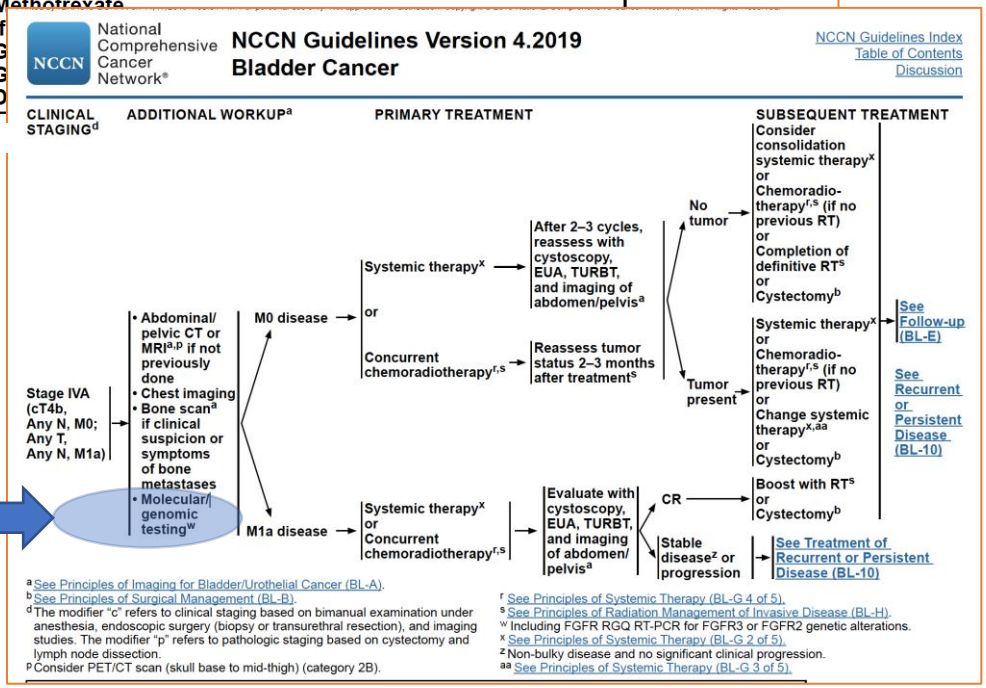
NCCN Guidelines Index
Table of Contents
Discussion

### PRINCIPLES OF SYSTEMIC THERAPY

| Subsequent systemic therapy for locally advanced or metastatic disease (Stage IV) (post-platinum)[c] Participation in clinical trials of new agents is recommended. | |
|---|---|
| **Preferred regimen**<br>• Pembrolizumab (category 1)[18] | **Other recommended regimens**<br>• Albumin-bound paclitaxel[27]<br>• Paclitaxel or docetaxel[25]<br>• Gemcitabine[14]<br>• Pemetrexed[26] |
| **Alternative preferred regimens**<br>• Atezolizumab[19]<br>• Nivolumab[20]<br>• Durvalumab[21]<br>• Avelumab[22,23]<br>• Erdafitinib[d,24] | **Useful in certain circumstances based on prior medical therapy**<br>• Ifosfamide[28]<br>• Methotrexate<br>• If<br>• G<br>• G<br>• D |

[d] Only for patients with susceptible *FGFR3* or *FGFR2* genetic alterations.

Is this the beginning of targeted therapy in mUC ?



# Vofatamab: an anti-FGFR3-specific Antibody

- Vofatamab (b-701) is a fully human, monoclonal antibody against FGFR3 that blocks activation of both WT and activating FGFR3 mut/fus

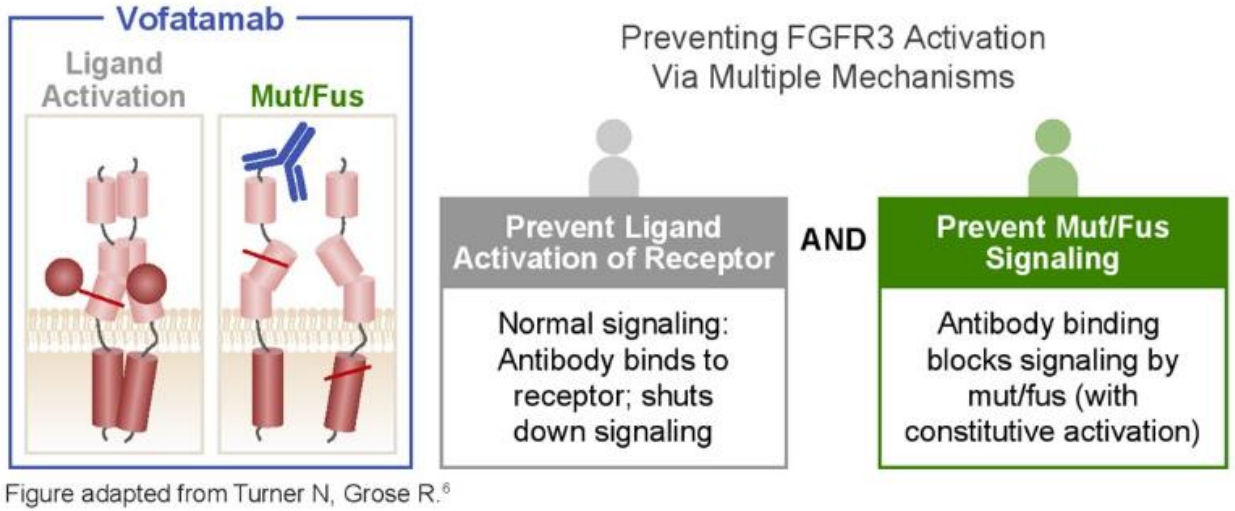
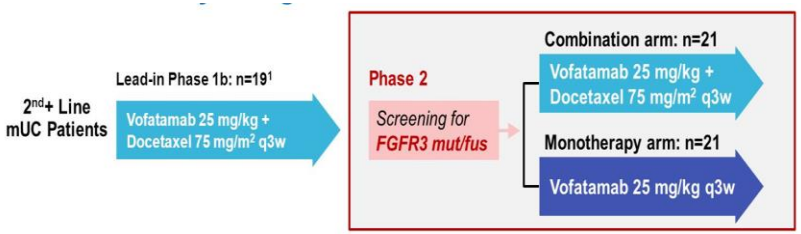



Figure adapted from Turner N, Grose R.[6]

Siefker-Radtke AO, et al. Poster presented at ASCO 2019. Abstract 4511.

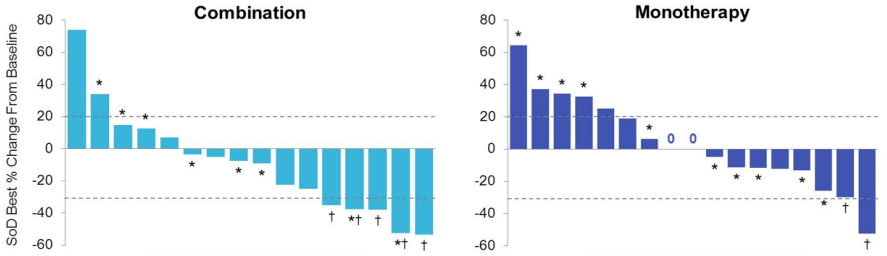
# VOFATAMAB: FIERCE-21

## FIERCE-21: Phase 2 Study of Vofatamab (B-701), a Selective Inhibitor of FGFR3, as Salvage Therapy in Metastatic Urothelial Carcinoma




## Efficacy: Best % Change From Baseline in SoD of Target Lesions

**Unconfirmed Responses per RECIST 1.1**




| Combination (3rd Line): n=21 | | Monotherapy (4th Line): n=21 |
|---|---|---|
| 2.6 | Median follow-up time, mo | 5.1 |
| 3.5 | Time to response, mo | 4 |
| NR | Median PFS, mo | 4 |
| 4 (27)* | DCR at 6 mo, n (%) | 4 (21) |

- Time to response too short to estimate ORR; study is ongoing

*Prior CPI use; †Best response of complete or partial response; censored n=9. Dashed lines indicate RECIST thresholds of +20% and -30%.
DCR, disease control rate; NR, not reached; SoD, sum of diameters. Initial analysis data cutoff: 12/21/18.

## Baseline Demographics and Treatment History of Patients

| | | Combination n=21 | Monotherapy n=21 |
|---|---|---|---|
| Baseline demographics | Male, n (%) | 19 (90) | 16 (76) |
| | Median age, y | 64 | 70 |
| | Ethnicity (white/Asian), n | 18 / 3 | 12 / 9 |
| | Median time from onset of mUC, mo | 10 | 17 |
| | ECOG 1, n (%) | 14 (67) | 14 (67) |
| | Bellmunt score, n (%) | | |
| | 0 | 5 (24) | 5 (24) |
| | 1 | 9 (43) | 12 (57) |
| | 2 | 7 (33) | 4 (19) |
| | Visceral / liver metastases, n (%) | 11 (52) / 5 (24) | 9 (43) / 4 (19) |
| Treatment history | Median no. of prior lines of therapy (range) | 2 (1–4) | 3 (1–7) |
| | ≥2 prior regimens, n (%) | 12 (57) | 15 (71) |
| | Prior CPI, n (%) | 11 (52) | 11 (52) |
| | PD as best response to prior therapy, n (%) | 14 (67) | 8 (38) |
| | Median time from most recent line, mo* | 1.3 | 1.6 |

*Time from most recent prior systemic therapy calculated as date of informed consent − date of most recent prior systemic therapy.
PD, progressive disease. Initial analysis data cutoff: 12/21/18.

## Most Common TEAEs Occurring in >20% of Patients

| MedDRA Preferred Term >20% of patients, n (%) | Total N=42 Any Grade | Combination: n=21 | | Monotherapy: n=21 | |
|---|---|---|---|---|---|
| | | Any Grade | ≥ Grade 3 | Any Grade | ≥ Grade 3 |
| Decreased appetite | 12 (29) | 6 (29) | 0 | 6 (29) | 0 |
| Diarrhea | 12 (29) | 9 (43) | 0 | 3 (14) | 0 |
| Pyrexia | 12 (29) | 5 (24) | 0 | 7 (33) | 0 |
| Asthenia | 9 (21) | 6 (29) | 0 | 3 (14) | 0 |
| Anemia | 9 (21) | 6 (29) | 4 (19) | 3 (14) | 2 (10) |
| Dyspnea | 9 (21) | 5 (24) | 1 (5) | 4 (19) | 1 (5) |
| Fatigue | 9 (21) | 6 (29) | 1 (5) | 3 (14) | 0 |

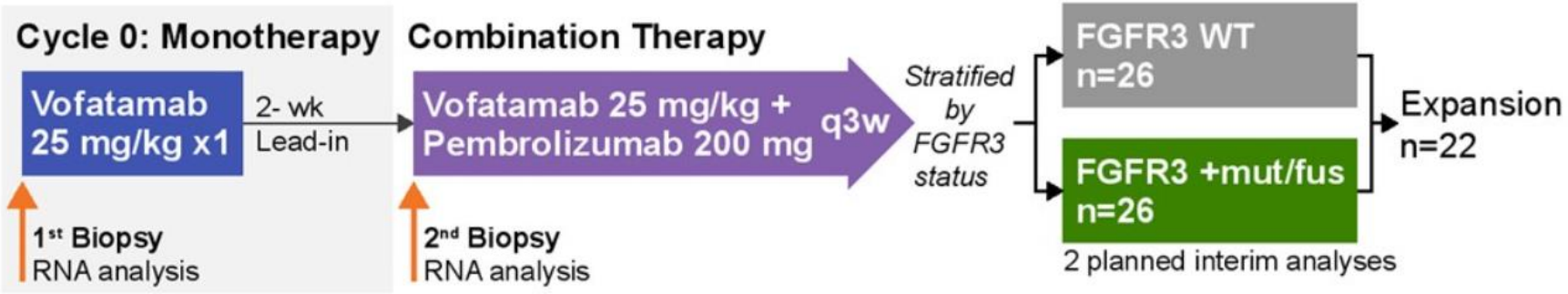
Initial analysis data cutoff: 12/21/18. MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent AE.

- Across the study the majority of patients described themselves as having good or better QoL on the PROMIS GPH T-Score after 3 cycles (57%), which was largely maintained through 6 cycles (55%).
- Most common vofatamab-related TEAEs were asthenia (21%), diarrhea (21%), decreased appetite (12%) and rash (12%); all were Grade 1 or 2.
- No cases of hyperphosphatemia or ocular or nail toxicity; 1 patient reported Grade 2 skin toxicity.

Necchi A, *et al.* J Clin Oncol 37, 2019 (suppl 7S; abstr 409). Presented at ASCO GU 2019.
Reproduced with permission from Dr A Necchi.

# FIERCE-22: Clinical activity of vofatamab a FGFR3 selective inhibitor in combination with pembrolizumab in WT mUC, preliminary analysis.

## Study desgin




Eligibility criteria: mUC pts with

- Progression on ≥1 line of prior platinum-based chemotherapy, or recurrence within ≤12 mo of (neo)adjuvant CT
- AntiPD-1/L1 naive
- Measurable disease
- ECOG <2

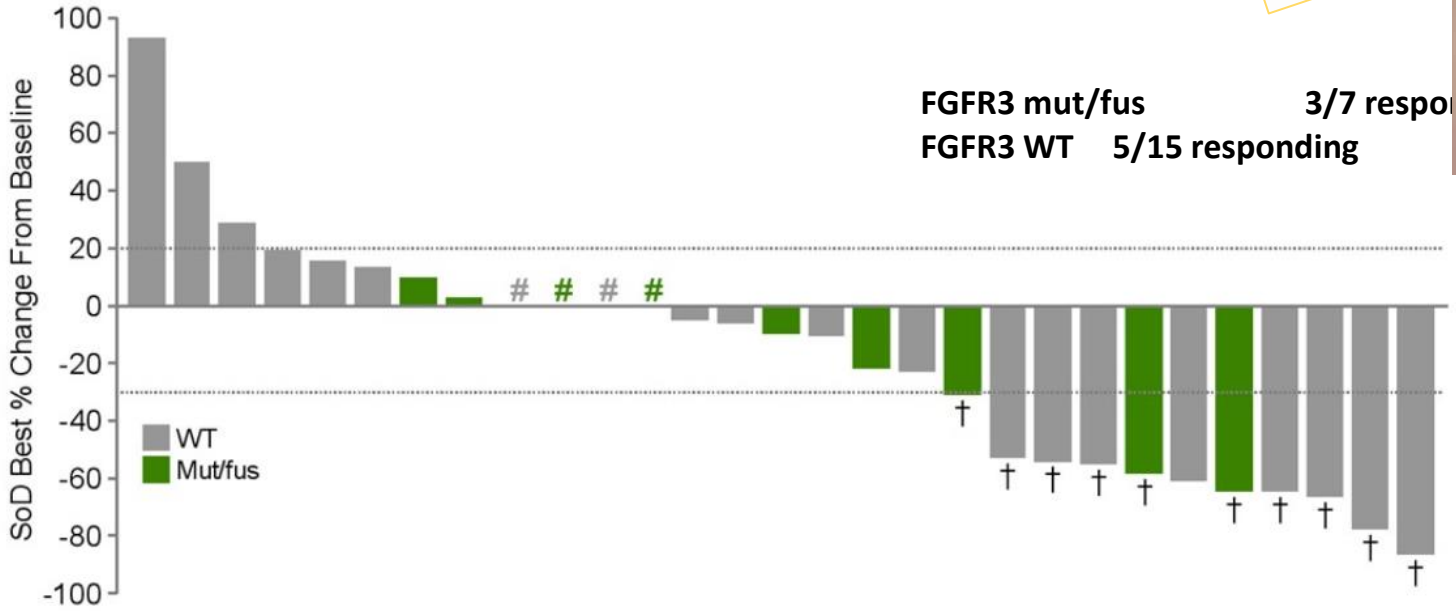
Data from 1st planned interim analysis after enrollment of 26 patients (data analysis cutoff 25 April 2019)

Siefker-Radtke AO, et al. Poster presented at ASCO 2019. Abstract 4511.

# Responses were similar regardless of FGFR3 Mut/Fus or WT status



**FGFR3 mut/fus** **3/7 respo**
**FGFR3 WT** **5/15 responding**




†Best response of complete or partial response (CR or PR); #No change from baseline. Dashed lines indicate RECIST 1.1 thresholds at +20% and -30%. SoD, sum of diameters.

Siefker-Radtke AO, et al. Poster presented at ASCO 2019. Abstract 4511.

# Potential Limitations to FGFR Inhibition

- **Low frequency** of the target?  **Timing** of molecular analysis
- Is the **DOR** long enough in the current setting?
- Is **safety** good enough compared with other treatment strategies?

# Lower frequency  in real world? Too long to get the information?

**PATIENTS**

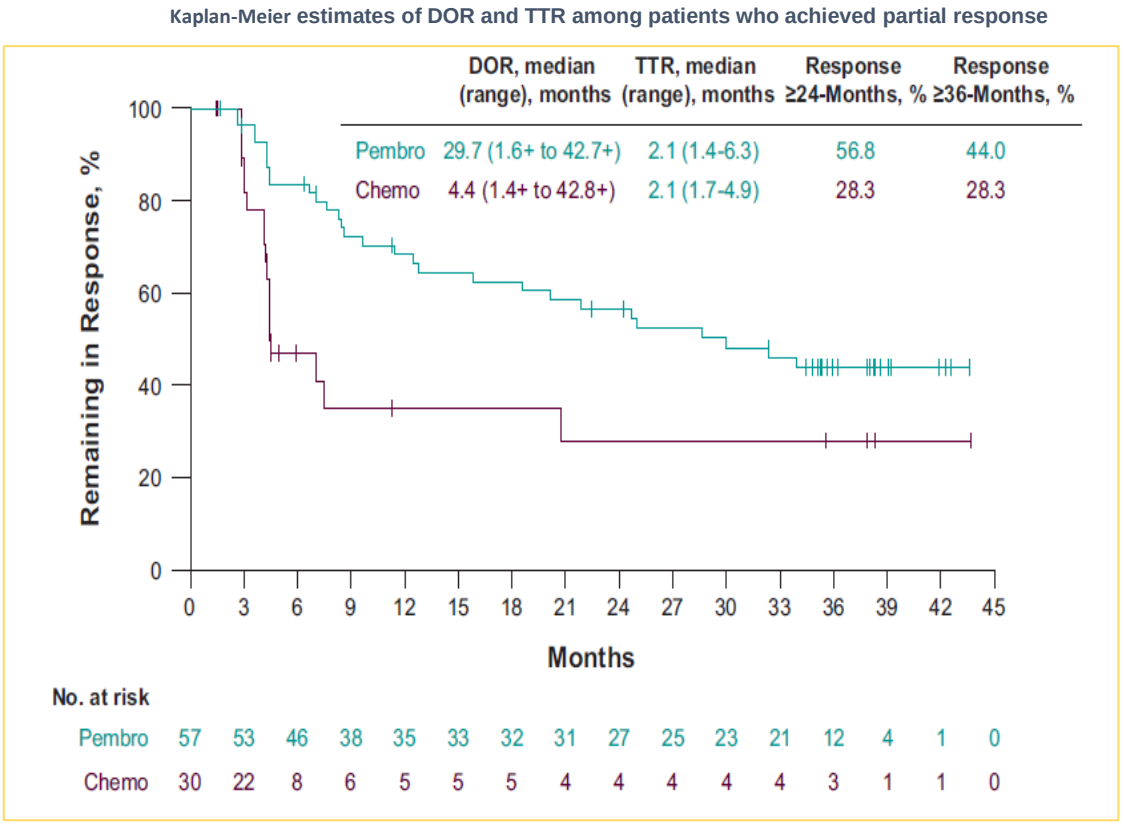
Between May 25, 2015, and March 15, 2018, we assessed 2214 patients for eligibility (Fig. S1 in the Supplementary Appendix). Of 210 eligible

- What is an aceptable delay in mUC?
- Can we improve FGFR analysis time?


Loriot Y et al. NEJM 2019

# DOR of other options

- IO has shown mDOR of over 2 and a half years w/ Pembrolizumab
- About 2 years with Atezolizumab



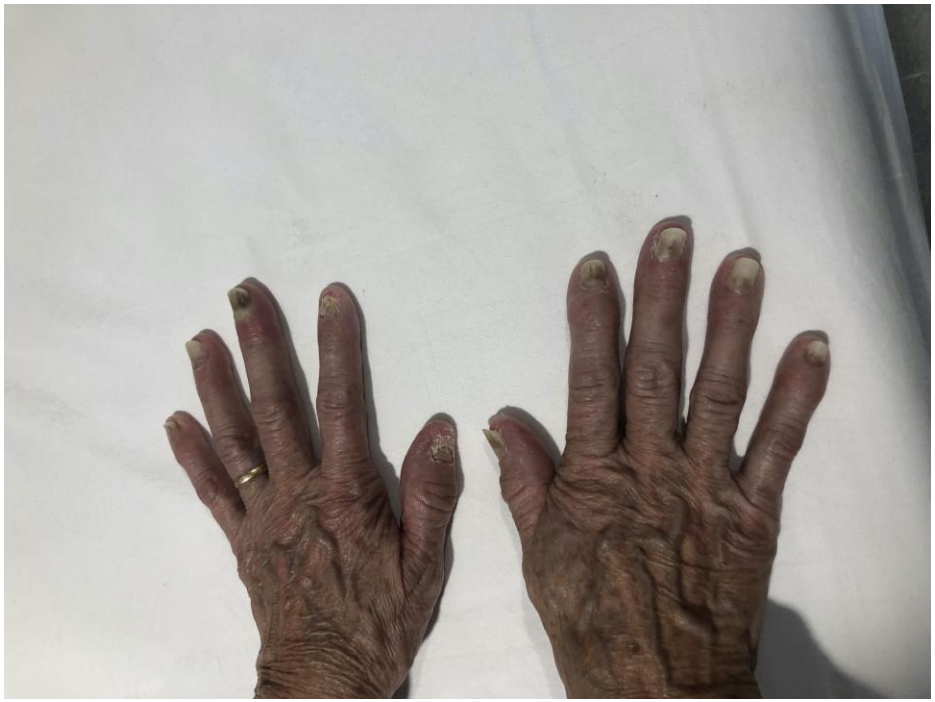

- Necchi A, et al. Poster presented at ESMO 2019; abstract 919P.

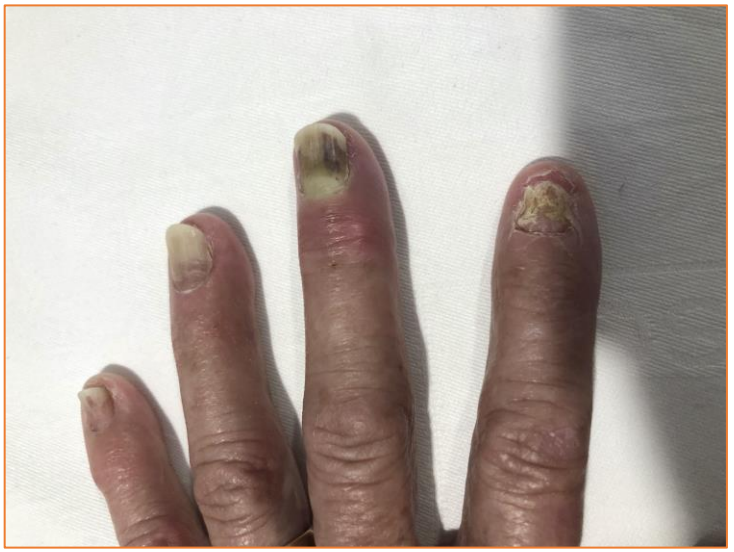
# Should Safety be an issue with FGFRi?

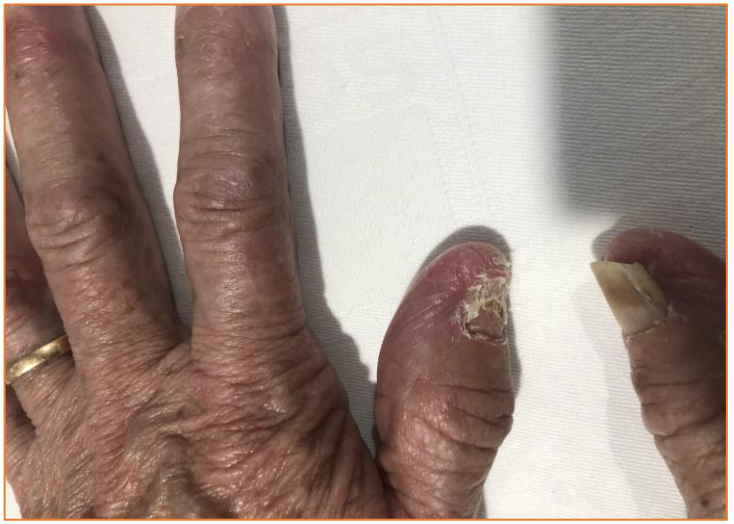
| Drug and disease Reference | Patients number | Toxicity | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | All toxicities | | HyperPh | | HypoPh | | Stomatitis | | Diarrhea | | Digestive tract events | | Nail events | | Hand-foot syndrome | | Ocular events | |
| | | Any G | G≥3 | Any G | G≥3 | Any G | G≥3 | Any G | G≥3 | Any G | G≥3 | Any G | G≥3 | Any G | G≥3 | Any G | G≥3 | Any G | G≥3 |
| Erdafitinib UC Loriot New Engl J Med 2019[39] | 99 | 100% | 46% | 77% | 2% | NR | | 58% | 10% | 51% | 4% | 30-40% | 1% | 18% | 2% | 23% | 5% | 19% | 3% |
| Infigratinib CCA Javle J Clin Oncol 2018[44] | 61 | 92% | 41% | 72% | 16% | 11% | 5% | 29% | 7% | 15% | 3% | 18% | 1% | 18% | / | 21% | 5% | 21% | / |
| Pemigatinib CCA / UC Hollebecque / Necchi ESMO 2018[41,46] | 89/108 | 93% | NR | 31% | 1% | 10% | 6% | 34% | 7% | 43% | 3% | 35% | 3% | NR | | NR | | 13% | 1% |
| Rogaratinib UC Joerger ASCO 2018[42] | 51 | NR | | 45% | / | NR | | NR | | 61% | 4% | 29% | 2% | NR | | NR | | NR | |
| Derazantinib CCA Mazzaferro Br J Cancer 2018[43] | 29 | 93% | 28% | 76% | 10% | NR | | 7% | 3% | 21% | / | 45% | 3% | NR | | NR | | 41% | 7% |
| AZD4547 NCI-MATCH Arm W Chae ASCO 2018[21] | 49 | 80% | 49% | NR | | NR | 2% | 22% | 14% | 20% | / | 24% | 2% | NR | | NR | 6% | NR | 2% |
| TAS-120, LY2874455, Debio 1347, BLU-554: Only phase I-dose finding data available | | | | | | | | | | | | | | | | | | | |

Table from Facchinetti F et al Clin Can Res 2019

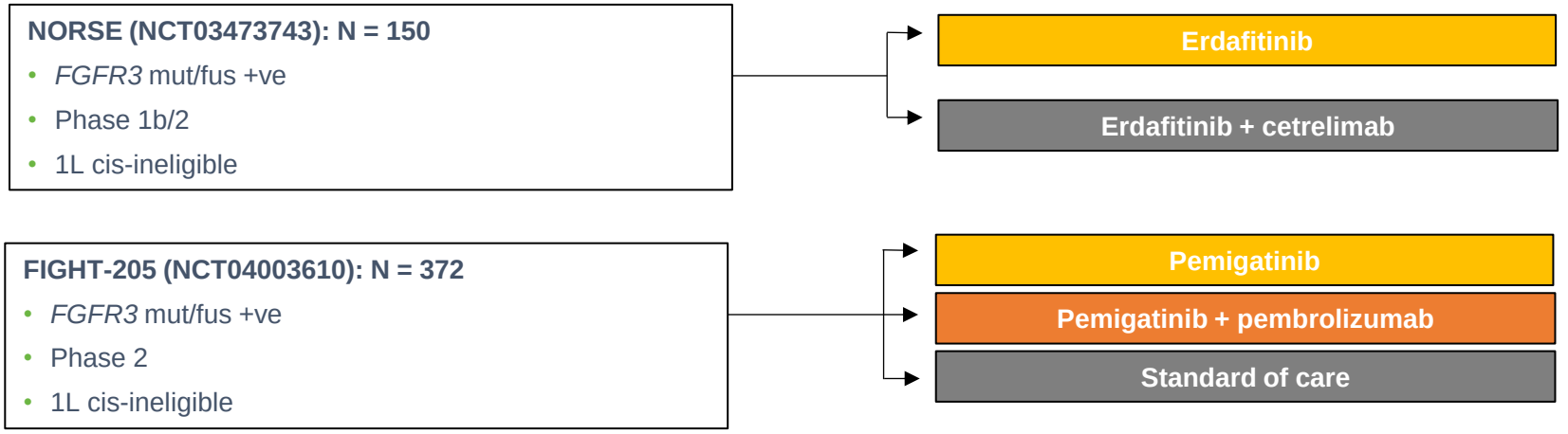
# A real case







# Near future in Drug Development of FGFRi



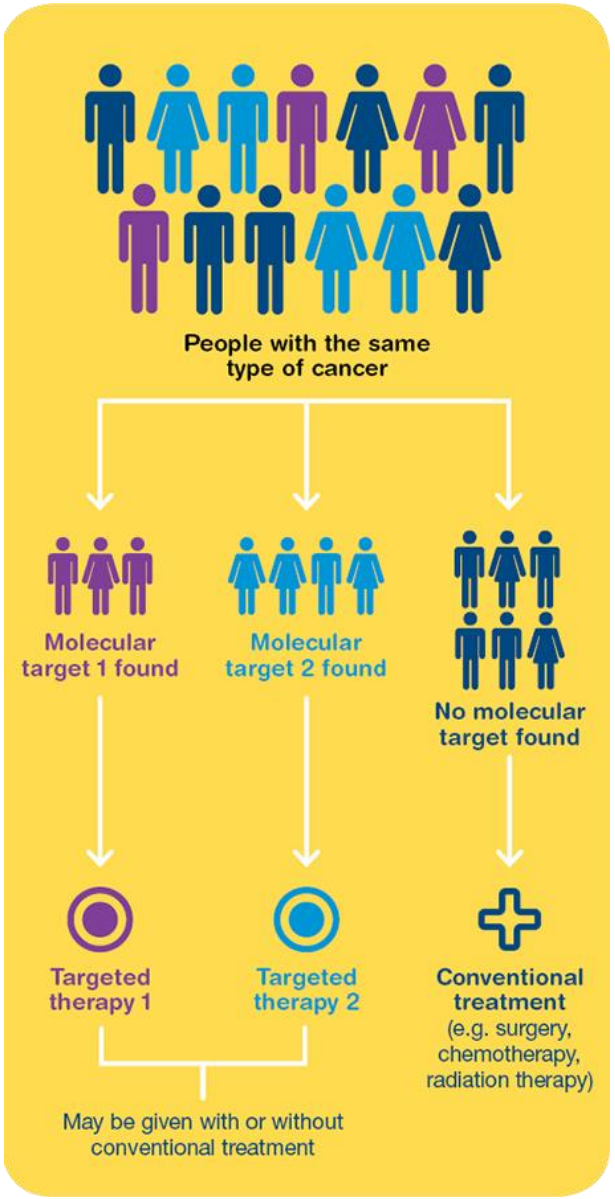

**THOR: Ongoing Phase 3 Study (N=630) of erdafitinib compared with chemotherapy or pembrolizumab**

**Studies in Non-Muscle invasive bladder cancer with Erdafitinib**

# Activity of FGFRi in development in Cholangiocarcinoma

| Reference | Patients treated | Objective responses | Stable Diseases | mPFS (mo) (95% CI) | mDOR (mo) (95% CI) | mDDC (mo) (95% CI) | mOS (mo) (95% CI) |
|---|---|---|---|---|---|---|---|
| Infigratinib Phase II<br>Javle J Clin Oncol 2018 [#43]<br>NCT02150967 | 61 $FGFR^{pos\#}$:<br>48 $FGFR2^{fused}$<br>8 $FGFR2^{mut}$<br>8 $FGFR1\text{-}3^{ampli}$ | 9 (15%)<br>All in $FGFR2^{fused}$ (19%) | 37( 61%)<br>31 (65%) | 5.8<br>(4.3-7.6) | 5.1<br>(3.9–7.4) | 7.5<br>(5.6-7.6) | / |
| Infigratinib Phase II<br>Javle ESMO 2018 [44§]<br>NCT02150967 | 71 $FGFR2^{fused}$ | 22 (31%) | 41 (58%) | 6.8<br>(5.3–7.6) | 5.4<br>(3.7–7.4) | | 12.5<br>(9.9–16.6) |
| Erdafitinib Phase I CCA patients<br>Balheda Clin Cancer Res 2019 [31]<br>NCT01703481 | 11 $FGFR^{pos}$:<br>8 $FGFR^{fused}$<br>3 $FGFR^{mut}$ | 3/11 (27%) | 3/11 (27%) | ≈ 5 | 11.4 | | |
| Derazantinib Phase II<br>Mazzaferro Br J Cancer 2018 [42]<br>NCT03230318 | 29 $FGFR2^{fused}$ | 6 (21%) | 18 (62%) | 5.7<br>(4.0–9.2) | 4.6<br>(2.3–8.9) | 5.8<br>(5.3–8.4) | Not reached<br>(mFU 20 mo) |
| Pemigatinib Phase II<br>Hollebecque ESMO 2018 [45]<br>NCT02924376 | Cohort A: $FGFR2^{fused}$: 47<br>Cohort B: Other FGF/FGFR driver: 22<br>Cohort C: No FGF/FGFR: 18 | A: 19 (40%)<br>B: 0<br>C: 0 | A: 21 (45%)<br>B: 10 (45%)<br>C: 4 (22%) | A: 9.2 (6.44-NE)<br>B: 2.1 (1.2-6.80)<br>C: 1.7 (1.4-1.8) | A: NE<br>(6.9-NE) | | A: 15.8<br>B: 6.8<br>C: 4 |
| TAS-120 Phase I CCA data<br>1) Tran<br>ESMO Asia 2018 [46]<br>2) Meric-Bernstam<br>ESMO GI 2018 [47]<br>NCT02052778 | 45 $FGFR^{pos}$ (41 iCCC):<br>8 $FGFR2^{fused}$<br>13 (29%) FGFR-TKI pretreated | $FGFR2^{fused}$: 7/24 (25%)<br>$FGFR2fusion^{neg}$: 3/17 (18%)<br>All in $FGFR2^{"rearranged"}$<br>4/13 (31%) in FGFR-TKI pretreated<br>(3 fused, 1 ampli) | $FGFR2^{fused}$: 15 (54%)<br>$FGFR2fusion^{neg}$: 10 (59%) | $FGFR2^{fused}$:<br>7.4 (4.8-NC)*<br>$FGFR2fusion^{neg}$:<br>6.8 (1.9-NC)* | / | / | / |
| Erdafitinib Phase IIa Asian<br>Park ASCO 2019 [48]<br>NCT02699606 | 34:<br>15 $FGFR2^{fused}$, 9 $FGFR2^{mut}$,<br>7 $FGFR3^{mut}$,$FGFR1^{fmut}$<br>out of 157 molecularly evaluable | 7/15 (47%)<br>$FGFR^{fused}$: 6/9 (67%) | 5/15 (33%)<br>$FGFR^{fused}$: 3/9 (33%) | 5.59<br>(1.91-12.65)<br>$FGFR^{fused}$: 12.65<br>(3.15-19.38) | 7.06<br>(3.6-12.2)<br>$FGFR^{fused}$: 7.29<br>(3.9-12.2) | / | / |

Table from Facchinetti F et al Clin Can Res 2019




# Targeted Therapy: Is there a real clinical evidence?

Is Targeted Therapy such as FGFR inhibition ready for Prime Time?

Are we overcoming some previously identified barriers ?

Is FGFR a good target for anti cancer treatment?

Limits to Personalized Cancer Medicine Tannock IF et al N Engl J Med 375;13; 2016

# Conclusions

- **FGFRi** seems to be a successful “targeted therapy” in some cancers

- The most solid data [along with drug/companion diagnostic test approval] is in **advanced urothelial tumours** with **Erdafitinib**

- Is it **time for a paradigm change** and start considering precision medicine in advanced bladder tumours?

- Despite this initial excitement some limitations apply to FGFRi such as **DOR**, **low prevalence of FGFR aberrations** and **safety profile** all this in a highly competitive environment

- There are **multiple ongoing studies** in the randomized setting that will more precisely define the real value of these compounds alone or in combination including trials in the NMI context


@nachoduranm